

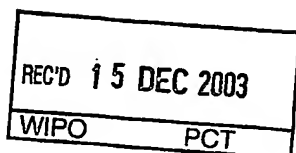


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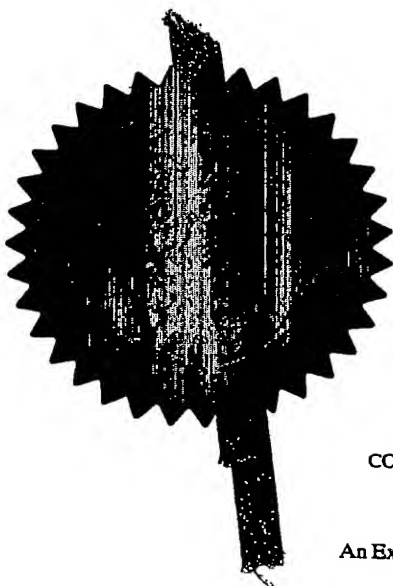
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*R. Mahoney*

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1.	Your reference	4-32758P1/NFI 8030	
2.	Patent application number (The Patent Office will fill in this part)	0226602.1	
3.	Full name, address and postcode of the or of each applicant (underline all surnames)	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND	
	Patent ADP number (if you know it)		
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND	
4.	Title of invention	Organic compounds	
5.	Name of your agent (if you have one)		
	"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH	
	Patents ADP number (if you know it)	1800001	
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority number (if you know it)
			Novartis Pharmaceuticals UK Ltd Patents and Trademarks Wimblehurst Road HORSHAM West Sussex RH12 5AB ADP No 0718522002
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:	Yes	
	a) any applicant named in part 3 is not an inventor, or		
	b) there is an inventor who is not named as an applicant, or		
	c) any named applicant is a corporate body.		
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**Patents Form 1/77**

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Description 17  
Claim(s) 2  
Abstract 1  
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Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

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11.

I/We request the grant of a patent on the basis of this application

Signature

Date

B. A. Yorke & Co

B.A. Yorke & Co.

14 November 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. J. Crook  
020 8560 5847

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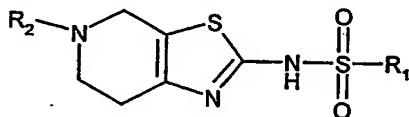
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**DUPLICATE****Organic Compounds**

The present invention relates to organic compounds, e.g. useful in the treatment of disorders mediated by the action of steroid sulfatase.

- 5 In one aspect the present invention provides a compound of formula



wherein

- R<sub>1</sub> is (C<sub>3-18</sub>)aryl, e.g. a phenyl, and  
 R<sub>2</sub> is (C<sub>1-12</sub>)alkoxycarbonyl, e.g. (C<sub>1-6</sub>)alkoxycarbonyl, such as tert.butoxycarbonyl;  
 10 (C<sub>1-4</sub>)alkylcarbonyl, such as (C<sub>3-5</sub>)cycloalkyl(C<sub>1-4</sub>)alkylcarbonyl, or unsubstituted or substituted phenyl, e.g. phenyl substituted by one or more groups as conventional in organic chemistry, such as phenyl substituted by one or more  
 - aminocarbonyl,  
 - halogen,  
 15 - (C<sub>1-6</sub>)haloalkyl.

A compound of formula I is an N-(3a,4,5,7,7a-hexahydro-thiazolo[5,4-c]pyridin-2-yl)-benzensulfonamide wherein the nitrogen atom of the pyridinyl group is substituted, e.g. by (C<sub>1-12</sub>)alkoxycarbonyl, (C<sub>1-4</sub>)alkylcarbonyl, such as (C<sub>3-5</sub>)cycloalkyl(C<sub>1-4</sub>)alkylcarbonyl, or by  
 20 phenyl substituted by one or more groups as conventional in organic chemistry, such as aminocarbonyl, halogen, (C<sub>1-6</sub>)haloalkyl.

- R<sub>1</sub> is (C<sub>3-18</sub>)aryl, substituted and unsubstituted a substituted (C<sub>3-18</sub>)aryl, such as a phenyl, e.g. phenyl substituted by one or more  
 25 - halogen  
 - (C<sub>1-6</sub>)haloalkyl, such as CF<sub>3</sub>.

In a compound of formula I preferably

- R<sub>1</sub> is phenyl substituted by one or more  
 30 - (C<sub>1-6</sub>)haloalkyl, such as CF<sub>3</sub>,  
 - halogen, and

R<sub>2</sub> is (C<sub>1-12</sub>)alkoxycarbonyl, e.g. (C<sub>1-6</sub>)alkoxycarbonyl, (C<sub>3-6</sub>)cycloalkyl(C<sub>1-4</sub>)alkylcarbonyl, or substituted phenyl, e.g. phenyl substituted by one or more

- aminocarbonyl,

- halogen,

5 - (C<sub>1-6</sub>)haloalkyl.

In another aspect the present invention provides a compound of formula I, which is selected from the group consisting of

2-[2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl]-4-trifluoromethyl-benzamide,

2-[2-(2,3-Dichloro-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl]-4-trifluoromethyl-benzamide,

2-[2-(3,5-Dichloro-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl]-4-trifluoromethyl-benzamide,

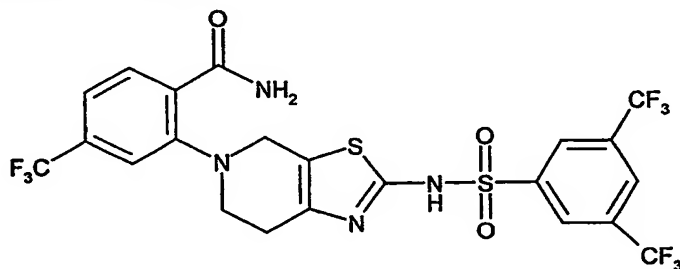
15 2-(3,5-Bis-trifluoromethyl-benzenesulfonamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester,

2-(2,3-Dichloro-benzenesulfonamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester,

2-(3,5-Dichloro-benzenesulfonamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester, and

20 N-[5-(2-Cyclopentyl-acetyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl]-3,5-bis-trifluoromethyl-benzenesulfonamide;

preferably a compound of formula



25 Compounds provided by the present invention are hereinafter designated as "compound(s) of (according to) the present invention". Each single substituent defined above in a compound of the present invention may be per se a preferred substituent, independently of the other substituents defined.

A compound of the present invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate.

- 5 In another aspect the present invention provides a compound of the present invention in the form of a salt.

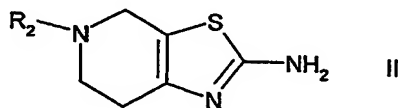
10 A salt of a compound of the present invention includes a pharmaceutically acceptable salt, e.g. including a metal salt, an acid addition salt. Metal salts include for example alkali or earth alkali salts; e.g. a sodium salt, acid addition salts include salts of a compound of the present invention with an acid, e.g. HCl.

15 A compound of the present invention in free form may be converted into a corresponding compound in the form of a salt; and vice versa. A compound of the present invention in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in unsolvated form; and vice versa.

20 A compound of the present invention may exist in the form of isomers and mixtures thereof. Isomeric, e.g. including enantiomeric or diastereomeric mixtures, may be separated as appropriate, e.g. according to a method as conventional, to obtain pure isomers. The present invention includes a compound of the present invention in any isomeric form and in any isomeric mixture.

25 Any compound described herein, e.g. including a compound of the present invention and intermediates in their preparation, may be prepared as appropriate, e.g. according, e.g. analogously, to a method as conventional, e.g. or as specified herein.

In another aspect the present invention provides a process for the production of a compound of the present invention comprising reacting an 4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-ylamine, e.g. of formula



30 wherein R<sub>2</sub> is as defined above, with a benzenesulfonylhalogenide, e.g. -chloride, such as a compound of formula R<sub>1</sub>-SO<sub>2</sub>Cl, wherein R<sub>1</sub> is as defined above, to obtain a compound of

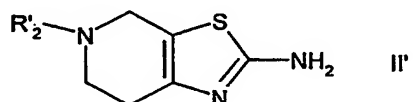
the present invention, such as an N-(3a,4,5,7,7a-hexahydro-thiazolo[5,4-c]pyridin-2-yl)-benzensulfonamide wherein the nitrogen atom of the pyridinyl group is substituted by (C<sub>1-12</sub>)alkoxycarbonyl, (C<sub>1-4</sub>)alkylcarbonyl, such as (C<sub>3-5</sub>)cycloalkyl(C<sub>1-4</sub>)alkylcarbonyl, or by phenyl substituted by one or more groups as conventional in organic chemistry, such as aminocarbonyl, halogen or (C<sub>1-6</sub>)haloalkyl, e.g. a compound of formula I.

The above reaction is an acylation reaction and may be carried out as appropriate, e.g. in appropriate solvent and at appropriate temperatures, e.g. according to a method as conventional or according to a method as described herein.

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Alternatively a compound of the present invention may be prepared by the following steps

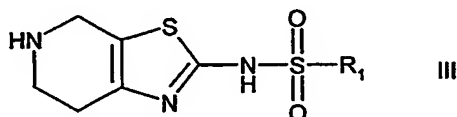
a. reacting of a compound of formula



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wherein R'<sub>2</sub> is tert-butoxycarbonyl, with a compound of formula R<sub>1</sub>-SO<sub>2</sub>Cl, wherein R<sub>1</sub> is as defined above, to obtain a compound of formula I, wherein R<sub>1</sub> is as defined above and R<sub>2</sub> is tert-butoxycarbonyl,

b. splitting off the tert-butoxycarbonyl group, e.g. by treatment with etheric HCl, to obtain a compound of formula



20

wherein R<sub>1</sub> is as defined above, e.g. in the form of a salt, such as a hydrochloride,

c. either reacting a compound of formula III

c1. with a (substituted) benzene fluoride to obtain a compound of formula I, wherein R<sub>1</sub> is as defined above and R<sub>2</sub> is a (substituted) phenyl, or

25

c2. with a (C<sub>3-5</sub>)cycloalkyl(C<sub>1-4</sub>)alkylcarbonylhalogenide, e.g. -chloride, to obtain a compound of formula I, wherein R<sub>1</sub> is as defined above and R<sub>2</sub> is (C<sub>3-5</sub>)cycloalkyl(C<sub>1-4</sub>)alkylcarbonyl, and

d. isolating a compound of formula I obtained from the reaction mixture.

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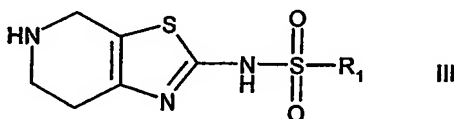
A compound of formula I may be converted in its sodium salt e.g. by treatment of a compound of formula i in free base form with NaOH, e.g. in EtOH, to obtain a compound of

formula I wherein the nitrogen of the sulfonamide group is in the form of an anion with Na as a cation.

A compound of formula II may be obtained as appropriate, e.g. according, e.g. analogously, to a method as conventional, e.g. by reacting an N-substituted piperidone with cyanamide in the presence of sulfur in a polar solvent, e.g. pyridine.

A compound of formula III is novel, e.g. useful as an intermediate for the preparation of a compound of formula I, and also forms part of the present invention.

In another aspect the present invention provides a compound of formula



wherein R<sub>1</sub> is as defined above, e.g. in the form of a salt, such as a hydrochloride, e.g. as an intermediate in the preparation of a compound of formula I.

Steroidal hormones in particular tissues are associated with several diseases, such as tumors of breast, endometrium and prostate and disorders of the pilosebaceous unit, e.g. acne, androgenetic alopecia, and hirsutism. Important precursors for the local production of these steroid hormones are steroid 3-O-sulfates which are desulfated by the enzyme steroid sulfatase in the target tissues. Inhibition of this enzyme results in reduced local levels of the corresponding active steroidal hormones, which is expected to be of therapeutic relevance.

Furthermore, steroid sulfatase inhibitors may be useful as immunosuppressive agents, and have been shown to enhance memory when delivered to the brain.

Acne is a polyetiological disease caused by the interplay of numerous factors, such as inheritance, sebum, hormones, and bacteria. The most important causative factor in acne is sebum production; in almost all acne patients sebaceous glands are larger and more sebum is produced than in persons with healthy skin. The development of the sebaceous gland and the extent of sebum production is controlled hormonally by androgens; therefore, androgens play a crucial role in the pathogenesis of acne. In man, there are two major sources supplying androgens to target tissues: (i) the gonades which secrete testosterone, (ii) the adrenals producing dehydroepiandrosterone (DHEA) which is secreted as the sulfate conjugate (DHEAS). Testosterone and DHEAS are both converted to the most active androgen, dihydrotestosterone (DHT), in the target tissue, e.g. in the skin. There is evidence that these pathways of local synthesis of DHT in the skin are more important than direct



supply with active androgens from the circulation. Therefore, reduction of endogeneous levels of androgens in the target tissue by specific inhibitors should be of therapeutic benefit in acne and seborrhoea. Furthermore, it opens the perspective to treat these disorders through modulation of local androgen levels by topical treatment, rather than influencing circulating hormone levels by systemic therapies.

Androgenetic male alopecia is very common in the white races, accounting for about 95% of all types of alopecia. Male-pattern baldness is caused by an increased number of hair follicles in the scalp entering the telogen phase and by the telogen phase lasting longer. It is a genetically determined hair loss effected through androgens. Elevated serum DHEA but normal testosterone levels have been reported in balding men compared with non-balding controls, implying that target tissue androgen production is important in androgenetic alopecia.

Hirsutism is the pathological thickening and strengthening of the hair which is characterized by a masculine pattern of hair growth in children and women. Hirsutism is androgen induced, either by increased formation of androgens or by increased sensitivity of the hair follicle to androgens. Therefore, a therapy resulting in reduction of endogeneous levels of androgens and/or estrogens in the target tissue (skin) should be effective in acne, androgenetic alopecia and hirsutism.

As described above, DHT, the most active androgen, is synthesized in the skin from the abundant systemic precursor DHEAS and the first step in the metabolic pathway from DHEAS to DHT is desulfatation of DHEAS by the enzyme steroid sulfatase to produce DHEA. The presence of the enzyme in keratinocytes and in skin-derived fibroblasts has been described. The potential use of steroid sulfatase inhibitors for the reduction of endogenous levels of steroid hormones in the skin was confirmed using known steroid sulfatase inhibitors, such as estrone 3-O-sulfamate and 4-methylumbelliferyl-7-O-sulfamate. We have found that inhibitors of placental steroid sulfatase also inhibit steroid sulfatase prepared from either a human keratinocyte (HaCaT) or a human skin-derived fibroblast cell line (1BR3GN). Such inhibitors were also shown to block steroid sulfatase in intact monolayers of the HaCaT keratinocytes.

Therefore, inhibitors of steroid sulfatase may be used to reduce androgen and estrogen levels in the skin. They can be used as inhibitors of the enzyme steroid sulfatase for the local treatment of androgen-dependent disorders of the pilosebaceous unit (such as acne, seborrhoea, androgenetic alopecia, hirsutism) and for the local treatment of squamous cell carcinoma.

Furthermore non-steroidal steroid sulfatase inhibitors are expected to be useful for the treatment of disorders mediated by the action of steroid hormones in which the steroidal products of the sulfatase cleavage play a role. Indications for these new kind of inhibitors include androgen-dependent disorders of the pilosebaceous unit (such as acne, seborrhea, androgenetic alopecia, hirsutism); estrogen- or androgen-dependent tumors, such as squamous cell carcinoma and neoplasms, e.g. of the breast, endometrium, and prostate; inflammatory and autoimmune diseases, such as rheumatoid arthritis, type I and II diabetes, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, thyroiditis, vasculitis, ulcerative colitis, and Crohn's disease, psoriasis, contact dermatitis, graft versus host disease, eczema, asthma and organ rejection following transplantation. Steroid sulfatase inhibitors are also useful for the treatment of cancer, especially for the treatment of estrogen- and androgen-dependent cancers, such as cancer of the breast and endometrium and squamous cell carcinoma, and cancer of the prostate. Steroid sulfatase inhibitors are also useful for the enhancement of cognitive function, especially in the treatment of senile dementia, including Alzheimer's disease, by increasing the DHEAS levels in the central nervous system.

Activities of compounds in inhibiting the activity of steroid sulfatase may be shown in the following test systems:

#### **Purification of human steroid sulfatase**

Human placenta is obtained freshly after delivery and stripped of membranes and connective tissues. For storage, the material is frozen at -70°C. After thawing, all further steps are carried out at 4°C, while pH values are adjusted at 20°C. 400 g of the tissue is homogenized in 1.2 l of buffer A (50 mM Tris-HCl, pH 7.4, 0.25 M sucrose). The homogenate obtained is centrifuged at 10,000xg for 45 minutes. The supernatant is set aside and the pellet obtained is re-homogenized in 500 ml of buffer A. After centrifugation, the two supernatants obtained are combined and subjected to ultracentrifugation (100,000xg, 1 hour). The pellet obtained is resuspended in buffer A and centrifugation is repeated. The pellet obtained is suspended in 50 ml of 50 mM Tris-HCl, pH 7.4 and stored at -20°C until further work-up.

After thawing, microsomes are collected by ultracentrifugation (as described above) and are suspended in 50 ml of buffer B (10 mM Tris-HCl, pH 7.0, 1 mM EDTA, 2 mM 2-mercaptoethanol, 1 % Triton X-100, 0.1 % aprotinin). After 1 hour on ice with gentle agitation, the suspension is centrifuged (100,000xg, 1 hour). The supernatant containing the

- enzyme activity is collected and the pH is adjusted to 8.0 with 1 M Tris. The solution obtained is applied to a hydroxy apatite column (2.6x20 cm) and equilibrated with buffer B, pH 8.0. The column is washed with buffer B at a flow rate of 2 ml/min. The activity is recovered in the flow-through. The pool is adjusted to pH 7.4 and subjected to
- 5 chromatography on a concanavalin A sepharose column (1.6x10 cm) equilibrated in buffer C (20 mM Tris-HCl, pH 7.4, 0.1 % Triton X-100, 0.5 M NaCl). The column is washed with buffer C, and the bound protein is eluted with 10 % methyl mannoside in buffer C. Active fractions are pooled and dialysed against buffer D (20 mM Tris-HCl, pH 8.0, 1 mM EDTA, 0.1 % Triton X-100, 10 % glycerol (v/v)).
- 10 The retentate obtained is applied to a blue sepharose column (0.8x10 cm) equilibrated with buffer D; which column is washed and elution is carried out with a linear gradient of buffer D to 2 M NaCl in buffer D. Active fractions are pooled, concentrated as required (Centricon 10), dialysed against buffer D and stored in aliquots at -20°C.

#### 15 **Assay of Human Steroid Sulfatase**

- It is known that purified human steroid sulfatase not only is capable to cleave steroid sulfates, but also readily cleaves aryl sulfates such as 4-methylumbelliferyl sulfate which is used in the present test system as an activity indicator. Assay mixtures are prepared by consecutively dispensing the following solutions into the wells of white microtiter plates:
- 20 1) 50 µl substrate solution (1.5 mM 4-methylumbelliferyl sulfate in 0.1 M Tris-HCl, pH 7.5)  
2) 50 µl test compound dilution in 0.1 M Tris-HCl, pH 7.5, 0.1 % Triton X-100 (stock solutions of the test compounds are prepared in DMSO; final concentrations of the solvent in the assay mixture not exceeding 1 %)  
3) 50 µl enzyme dilution (approximately 12 enzyme units/ml)
- 25 We define one enzyme unit as the amount of steroid sulfatase that hydrolyses 1 nmol of 4-methylumbelliferyl sulfate per hour at an initial substrate concentration of 500 µM in 0.1 M Tris-HCl, pH 7.5, 0.1 % Triton X-100, at 37°C.
- Plates are incubated at 37°C for 1 hour. Then the reaction is stopped by addition of 100 µl 0.2 M NaOH. Fluorescence intensity is determined in a Titertek Fluoroskan II instrument with
- 30  $\lambda_{\text{ex}} = 355 \text{ nm}$  and  $\lambda_{\text{em}} = 460 \text{ nm}$ .

#### **Calculation of relative IC<sub>50</sub> values**

From the fluorescence intensity data (I) obtained at different concentrations (c) of the test compound in the human steroid sulfatase assay as described above, the concentration inhibiting the enzymatic activity by 50 % (IC<sub>50</sub>) is calculated using the equation:

$$I = \frac{I_{100}}{1 + (c / IC_{50})^s}$$

wherein I<sub>100</sub> is the intensity observed in the absence of inhibitor and s is a slope factor. Estrone sulfamate is used as a reference compound and its IC<sub>50</sub> value is determined in parallel to all other test compounds. Relative IC<sub>50</sub> values are defined as follows:

$$\text{rel IC}_{50} = \frac{\text{IC}_{50} \text{ of test compound}}{\text{IC}_{50} \text{ of estrone sulfamate}}$$

According to our testing and calculation estrone sulfamate shows an IC<sub>50</sub> value of approximately 60 nM.

The compounds of the present invention show activity in that described assay.

#### CHO/STS Assay

CHO cells stably transfected with human steroid sulfatase (CHO/STS) are seeded into microtiter plates. After reaching approximately 90% confluency, they are incubated overnight with graded concentrations of test substances (e.g. compounds of the present invention). They are then fixed with 4% paraformaldehyde for 10 minutes at room temperature and washed 4 times with PBS, before incubation with 100 µl/well 0.5 mM 4-methylumbelliferyl sulfate (MUS), dissolved in 0.1M Tris-HCl, pH 7.5. The enzyme reaction is carried out at 37°C for 30 minutes. Then 50 µl/well stop solution (1M Tris-HCl, pH 10.4) are added. The enzyme reaction solutions are transferred to white plates (Microfluor, Dynex, Chantilly, VA) and read in a Fluoroskan II fluorescence microtiter plate reader. Reagent blanks are subtracted from all values. For drug testing, the fluorescence units (FU) are divided by the optical density readings after staining cellular protein with sulforhodamine B (OD<sub>550</sub>), in order to correct for variations in cell number. IC<sub>50</sub> values are determined by linear interpolation between two bracketing points. In each assay with inhibitors, estrone 3-O-sulfamate is run as a reference compound, and the IC<sub>50</sub> values are normalized to estrone 3-O-sulfamate (relative IC<sub>50</sub> = IC<sub>50</sub> compound / IC<sub>50</sub> estrone 3-O-sulfamate).

The compounds of the present invention show activity in that described assay.

**Assay Using Human Skin Homogenate**

Frozen specimens of human cadaver skin (about 100 mg per sample) are minced into small pieces (about 1x1 mm) using sharp scissors. The pieces obtained are suspended in ten volumes (w/w) of buffer (20 mM Tris-HCl, pH 7.5), containing 0.1 % Triton X-100. Test

- 5 compounds (e.g. compounds of the present invention) are added at graded concentrations from stock solutions in ethanol or DMSO. Second, DHEAS as the substrate is added (1  $\mu$ C/ml [ $^3$ H]DHEAS, specific activity: about 60 Ci/mmol, and 20  $\mu$ M unlabeled DHEAS). Samples are incubated for 18 hrs at 37°C. At the end of the incubation period, 50  $\mu$ l of 1 M Tris, pH 10.4 and 3 ml of toluene are added. A 1-ml aliquot of the organic phase is removed
- 10 and subjected to liquid scintillation counting. The determined dpm-values in the aliquots are converted to nmol of DHEA cleaved per g of skin per hour.

The compounds of the present invention show activity in that described assay.

- The compounds of the present invention show activity in test systems as defined above. A
- 15 compound of the present invention in salt and/or solvate form exhibits the same order of activity as a compound of the present invention in free and/or non-solvated form.

The compounds of the present invention are therefore indicated for use as steroid sulfatase inhibitors in the treatment of disorders mediated by the action of steroid sulfatase, e.g. including androgen-dependent disorders of the pilosebaceous unit, such as

- 20 - acne,  
- seborrhea,  
- androgenetic alopecia,  
- hirsutism;  
- cancers, such as estrogen and androgen-dependent cancers;
- 25 - cognitive dysfunctions, such as senile dementia including Alzheimer's disease.

The compounds of the present invention are preferably used in the treatment of acne, seborrhea, androgenetic alopecia, hirsutism; estrogen, e.g. and androgen-dependent cancers, more preferably in the treatment of acne. Treatment includes therapeutical treatment and prophylaxis.

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The use of n N-(3a,4,5,7,7a-hexahydro-thiazolo[5,4-c]pyridin-2-yl)-benzensulfonamide wherein the nitrogen atom of the pyridinyl group is substituted, e.g. by (C<sub>1-12</sub>)alkoxycarbonyl, (C<sub>1-4</sub>)alkylcarbonyl, such as (C<sub>3-5</sub>)cycloalkyl(C<sub>1-4</sub>)alkylcarbonyl, or by phenyl substituted by one or more groups as conventional in organic chemistry, such as aminocarbonyl, halogen

or (C<sub>1-8</sub>)haloalkyl, e.g. a compound of the present invention, as steroid sulfatase inhibitor is novel.

5 In another aspect the present invention provides the use of an N-(3a,4,5,7,7a-hexahydro-thiazolo[5,4-c]pyridin-2-yl)-benzensulfonamide wherein the nitrogen atom of the pyridinyl group is substitute, e.g. a compound of the present invention, in the preparation of a medicament for the treatment of a disorder mediated by the action of steroid sulfatase, e.g. a disorder responsive to the inhibition of the action of steroid sulfatase, most preferably acne.

10 In another aspect the present invention provides a compound of formula I for use as a pharmaceutical, e.g. in the treatment of disorders mediated by the action of steroid sulfatase.

15 In another aspect the present invention provides a method of treating disorders mediated by the action of steroid sulfatase comprising administering a therapeutically effective amount of a compound of the present invention, e.g. a compound of formula I, to a subject in need of such treatment.

20 For such use the dosage to be used will vary, of course, depending e.g. on the particular compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results may be obtained if the compounds are administered at a daily dose of from about 0.1 mg/kg to about 100 mg/kg animal body weight, e.g. conveniently administered in divided doses two to four times daily. For most large mammals the total daily dosage is from about 5 mg to about 5000 mg, conveniently administered, for example, in divided doses up to four times a day or in retarded form. Unit dosage forms comprise, e.g.

25 from about 1.25 mg to about 2000 mg of a compound of a present invention in admixture with at least one pharmaceutically acceptable excipient, e.g. carrier, diluent.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt, e.g. an acid addition salt or metal salt; or in free form; optionally in the form of a solvate.

30 The compounds of the present invention may be administered in similar manner to known standards for use in such indications. The compounds of the present invention may be admixed with conventional, e.g. pharmaceutically acceptable, excipients, such as carriers and diluents and optionally further excipients. The compounds of the present invention may be administered, e.g. in the form of pharmaceutical compositions,

- orally, e.g. in the form of tablets, capsules;
- parenterally, intravenously, e.g. in the form of liquids, such as solutions, suspensions;
- topically, e.g. in the form of ointments, creams.

The concentrations of the active substance in a pharmaceutical composition will of course vary, e.g. depending on the compound used, the treatment desired and the nature of the composition used. In general, satisfactory results may be obtained at concentrations of from about 0.05 to about 5 % such as from about 0.1 to about 1% w/w in topical compositions, and by about 1% w/w to about 90% w/w in oral, parenteral or intravenous compositions.

In another aspect the present invention provides a pharmaceutical composition comprising a pharmaceutically effective amount of at least one compound of the present invention in association with at least one pharmaceutically acceptable excipient.

A pharmaceutical composition of the present invention may comprise as an active ingredient one or more compounds of the present invention, e.g. at least one, and one or more other pharmaceutically active agents. At least one compound of the present invention thus may be used for pharmaceutical treatment alone, or in combination with one or more further pharmaceutically active agents. Such further pharmaceutically active agents include e.g. retinoids, e.g. retinoic acid, such as isotretinoin; tretinoin (Roche); adapalene (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid); oral contraceptives, e.g. 19- nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20-in-3,17-diol, 6-Chlor-17-hydroxy-1 $\alpha$ ,2 $\alpha$ -methylen-4,6- pregnadien-3,20- dion, such as Diane® (Schering), antibacterials, such as erythromycins, including erythromycin A, azithromycin, clarithromycin, roxythromycin; tetracyclines, lincosamid-antibiotics, such as clindamycin (methyl 7-chlor-6,7,8-tridesoxy-6-(trans-1-methyl-4-propyl-L-2-pyrrolidin-carboxamido)-1-thio-L-threo- $\alpha$ -D-galacto-octopyranosid), azelaic acid (nonanedionic acid), nadifloxacin; dapson, benzoyl peroxide; keratolytics, such as salicylic acid; anti-inflammatory agents, such as corticosteroids, pimecrolimus; steroid 5 $\alpha$ -reductase inhibitors.

For the treatment of breast and endometrial cancer further pharmaceutically active agents include aromatase inhibitors, such as anastrozole, letrozole, exemestane.

Combinations include

- fixed combinations, in which two or more pharmaceutically active agents are in the same pharmaceutical composition,

- kits, in which two or more pharmaceutically active agents in separate compositions are sold in the same package, e.g. with instruction for co-administration; and
- free combinations in which the pharmaceutically active agents are packaged separately, but instruction for simultaneous or sequential administration are given.

5

In another aspect the present invention provides a compound of the present invention in combination with at least one other pharmaceutically effective agent for use as a pharmaceutical, such as a pharmaceutical composition comprising a combination of at least one compound of the present invention with at least one other pharmaceutically effective agent in association with at least one pharmaceutical acceptable excipient.

10

In the following example, which illustrate the invention references to temperature are in degree Centigrade and are uncorrected.

The following abbreviations are used:

15

m.p.: melting point

EtAc: ethyl acetate

BOC: tert-butyloxycarbonyl

RT: room temperature

DMSO: dimethylsulfoxide

20

DMAP: N,N-dimethylaminopyridine

DIEA: diisopropylethylamine



**Example 1****2-[2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo-[5,4-c]pyridin-5-yl]-4-trifluoromethyl-benzamide****A. Free base**

- 5 3.3 g of 2-(3,5-bis-trifluoromethyl-benzenesulfonylamino)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-5-ium hydrochloride, 1.545 g of 2-fluoro-4-trifluoromethyl-benzamide, and 3.3 g of  $K_2CO_3$  are heated in DMSO at 150 ° for 5 hours. From the mixture obtained solvent is evaporated, the evaporation residue obtained is dissolved in EtAc/MeOH (9/1) and the mixture obtained is extracted with 50 ml of 1 M HCl and brine. Two phases are obtained and are
- 10 separated and the organic layer obtained is concentrated and subjected to chromatography. 2-[2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo-[5,4-c]pyridin-5-yl]-4-trifluoromethyl-benzamide is obtained and is re-crystallized from EtAc.
- m.p.: 225-228 °;  $^1H$ -NMR /  $CD_3OD$ : 8.35 (s, 2 H), 8.03 (s, 1 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.40 (dd, J = 8.0, 1.1 Hz, 1 H), 7.35 (s, 1 H), 4.06 (t, J = 1.8 Hz, 2 H), 3.44 (t, J = 5.6 Hz, 2
- 15 H), 2.69 (m, 2 H);  $^{13}C$ -NMR /  $CD_3OD$ : 168.83, 149.35, 144.47, 133.37, 133.11, 131.99, 131.72, 131.08, 130.83, 126.07, 124.89, 123.27, 119.90, 116.27, 116.24, 113.20, 49.44, 47.90, 22.76.

**B. Sodium salt**

- To a solution of 118 mg of 2-[2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo-[5,4-c]pyridin-5-yl]-4-trifluoromethyl-benzamide in 10 ml of ethanol 1.9 ml of an
- 20 aqueous 0.1M NaOH solution are added and the mixture obtained is stirred at RT for 5 minutes. From the mixture obtained solvent is evaporated and the evaporation residue obtained is subjected to lyophilisation from dioxane. [2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo-[5,4-c]pyridin-5-yl]-4-trifluoromethyl-
- 25 benzamide sodium salt is obtained.  $^1H$ -NMR/  $CDCl_3/CD_3OD$ : 8.45 (s, 2 H), 8.03 (d, J = 7.9 Hz, 1 H), 7.94 (s, 1 H), 7.43 (d, J = 7.9 Hz, 1 H), 7.42 (s, 1 H), 4.08 (s, 2 H), 3.44 (t, J = 5.7 Hz, 2 H), 2.74 (t, J = 5.6 Hz, 2 H);  $^{13}C$ -NMR/  $CDCl_3/CD_3OD$ : 168.92, 168.35, 151.59, 146.76, 141.82, 134.49, 134.17, 132.56, 132.30, 132.22, 131.89, 131.55, 130.91, 127.55, 125.16, 124.60, 122.45, 121.95, 120.89, 117.75, 115.34, 51.78, 50.04, 26.71.

30

Analogously to the method as described in example 1A, but using appropriate starting materials, the compounds of examples 2 and 3 are obtained:

**Example 2**

**2-[2-(2,3-Dichloro-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl]-4-trifluoromethyl-benzamide**

<sup>13</sup>C-NMR: 168.92, 168.81, 150.39, 142.57, 135.40, 134.21, 133.35, 132.01, 131.02, 129.24, 128.11, 120.15, 117.01, 113.68, 50.35, 48.84, 24.27.

5

**Example 3****2-[2-(3,5-Dichloro-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl]-4-trifluoromethyl-benzamide**

<sup>13</sup>C-NMR: 168.64, 154.30, 145.48, 135.73, 132.77, 132.43, 127.25, 125.62, 115.24, 81.45, 52.24, 49.95, 34.89, 33.98, 31.79, 28.71.

10

**Example 4****2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester**

15 A mixture of 8.5 g of 2-amino-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester, 15.6 g of 3,5-bis-trifluoromethyl-benzenesulfonyl chloride, and 8.1 g of DMAP in 100 ml of pyridine is stirred at 80° for 4 hours. From the mixture obtained solvent is evaporated, the evaporation residue is treated with EtAc and the mixture obtained is extracted with aqueous NaHSO<sub>4</sub> solution and brine. The organic layer obtained is dried, from  
20 the solution obtained solvent is removed and the residue obtained is treated with a mixture of EtAc and c-Hex (1:2 + 5% MeOH). 2-(3,5-bis-trifluoromethyl-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester precipitates, is filtrated off and dried. <sup>1</sup>H-NMR/CDCl<sub>3</sub>: 11.40 (bs, 1 H), 8.31 (s, 2 H), 8.03 (s, 1 H), 4.39 (s, 2 H), 3.72 (t, J = 5.5 Hz, 2 H), 2.78 (t, J = 5.6 Hz, 2 H), 1.48 (s, 9 H); <sup>13</sup>C-NMR/CDCl<sub>3</sub>: 169.79, 154.58,  
25 144.23, 133.52, 133.18, 132.84, 132.50, 131.61, 127.26, 126.97, 126.34, 124.25, 121.54, 118.82, 81.48, 28.68, 24.04.

25

Analogously to the method as described in example 4, but using appropriate starting materials, the compounds of examples 5 and 6 are obtained:

30

**Example 5****2-(2,3-Dichloro-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester**

<sup>13</sup>C-NMR: 169.71, 140.50, 136.08, 134.48, 131.98, 130.93, 129.81, 127.26, 81.29, 28.72, 24.25.

#### Example 6

- 5    **2-(3,5-Dichloro-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester**

<sup>13</sup>C-NMR: 169.84, 154.65, 136.16, 132.79, 131.63, 125.46, 81.45, 28.73, 24.16.

#### Example 7

- 10    **N-[5-(2-Cyclopentyl-acetyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl]-3,5-bis-trifluoromethyl-benzenesulfonamide**

DIEA and cyclopentylacetylchloride are added at 0°C to a mixture of 75 mg of 2-(3,5-bis-trifluoromethyl-benzenesulfonylamino)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-5-ium hydrochloride salt in CH<sub>2</sub>Cl<sub>2</sub>. The mixture obtained is stirred at RT for 4 hours, 2 ml of 1 M aqueous NaHSO<sub>4</sub> solution are added and two phases formed are separated. The organic layer obtained is concentrated and subjected to preparative HPLC (RP-18). N-[5-(2-Cyclopentyl-acetyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl]-3,5-bis-trifluoromethyl-benzenesulfonamide is obtained. <sup>1</sup>H-NMR/ CDCl<sub>3</sub> (2 rotamers): 12.3 (bs, 1 H), 8.28 (s, 2 H), 7.92 (s, 1 H), 4.44 (s, 1.2 H), 4.32 (s, 0.8 H), 3.79 (t, J = 5.5 Hz, 0.8 H), 3.16 (t, J = 5.6 Hz, 1.2 H), 2.55 (m, 1.2 H), 2.48 (m, 0.8 H), 2.32 (t, J = 6.3 Hz, 1.2 H), 2.17 (m, 1 H), 1.78 (m, 2 H), 1.52 (m, 4 H), 1.07 (m, 2 H); <sup>13</sup>C-NMR/ CDCl<sub>3</sub>: 172.12, 168.95, 145.48, 132.84, 132.50, 129.85, 127.03, 125.64, 124.40, 121.68, 114.06, 43.27, 42.49, 40.41, 40.18, 39.69, 38.65, 36.90, 33.08, 25.28, 24.44, 23.37.

- 25    **Preparation of starting materials**

**S1. 2-Amino-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester (compound of formula II' wherein R'<sub>2</sub> is tert-butoxycarbonyl)**

- A mixture of 19.9 g of 1-BOC-4-piperidone, 8.4 g of cyanamide, and 6.4 g of sulfur in 100 ml of pyridine is refluxed under inert atmosphere for 100 minutes. From the mixture obtained solvent is evaporated and the evaporation residue obtained is subjected to flash chromatography over silica gel. 2-Amino-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester is obtained in the form of an amorphous solid.

<sup>1</sup>H-NMR/CDCl<sub>3</sub>/d<sub>6</sub>-DMSO: 5.95 (bs, 2 H), 4.39 (s, 2 H), 3.67 (t, J = 5.2 Hz, 2 H), 3.08 (bs, 2 H), 1.43 (s, 9 H); <sup>13</sup>C-NMR/ CDCl<sub>3</sub>/d<sub>6</sub>-DMSO: 166.17, 153.87, 79.19, 28.86, 27.69, 26.01

**S2. 2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-5-ium hydrochloride salt (compound of formula III, wherein R<sub>1</sub> is 3,5-trifluoromethylbenzene)**

- 5 50 ml of saturated etheric hydrochloric acid are added to a solution of 9.95 g of 2-(3,5-bis-trifluoromethyl-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid tert-butyl ester in 150 ml of CH<sub>2</sub>Cl<sub>2</sub> and the mixture obtained is stirred at RT for 4 hours. From the mixture obtained solvent is evaporated and the evaporation residue obtained is treated with diethylether. A solid precipitates, is filtrated off and dried.
- 10 2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-5-ium hydrochloride salt is obtained in crystalline form.
- <sup>1</sup>H-NMR/ CDCl<sub>3</sub>/d<sub>6</sub>-DMSO: 13.30 (bs, 1 H), 9.86 (bs, 2 H), 8.43 (s, 2 H), 8.29 (s, 1 H), 4.04 (s, 2 H), 3.21 (t, J = 5.8 Hz, 2 H), 2.70 (t, J = 5.7 Hz, 2 H); <sup>13</sup>C-NMR/ CDCl<sub>3</sub>/d<sub>6</sub>-DMSO: 168.35, 145.15, 132.17, 131.83, 131.50, 131.17, 130.20, 127.02, 126.66, 126.47, 124.31, 121.59, 118.87, 109.47, 20.30.
- 15

Analogously as described in example S2, but using appropriate starting materials, the compounds of examples S3 and S4 are obtained:

**S3. 2-(2,3-Dichloro-benzenesulfonylamino)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-5-ium hydrochloride salt (compound of formula III, wherein R<sub>1</sub> is 2,3-dichlorobenzene)**

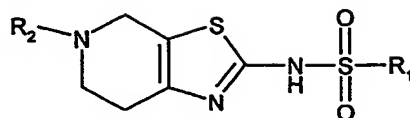
<sup>13</sup>C-NMR: 168.03, 141.31, 134.17, 134.06, 129.33, 129.23, 128.56, 128.33, 108.80, 19.95.

**S4. 2-(3,5-Dichloro-benzenesulfonylamino)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-5-ium hydrochloride salt (compound of formula III, wherein R<sub>1</sub> is 3,5-dichlorobenzene)**

<sup>13</sup>C-NMR: 168.03, 141.31, 134.17, 134.06, 129.33, 129.23, 128.56, 128.33, 108.80, 19.95.

# Patent claims

1. A compound of formula



5 wherein

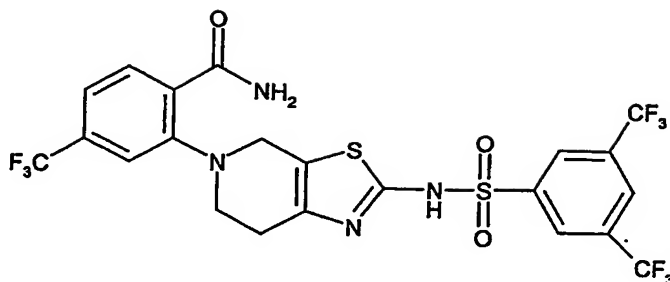
R<sub>1</sub> is (C<sub>3-18</sub>)aryl, and

R<sub>2</sub> is (C<sub>1-12</sub>)alkoxycarbonyl, (C<sub>1-4</sub>)alkylcarbonyl, or unsubstituted or substituted phenyl,  
e.g. phenyl substituted by one or more groups selected from the group consisting of

- aminocarbonyl,
- 10 - halogen,
- (C<sub>1-6</sub>)haloalkyl.

2. A compound according to claim 1 which is selected from the group consisting of
  - 2-[2-(3,5-Bis-trifluoromethyl-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-
  - 15 c]pyridin-5-yl]-4-trifluoromethyl-benzamide,
  - 2-[2-(2,3-Dichloro-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl]-4-
  - trifluoromethyl-benzamide,
  - 2-[2-(3,5-Dichloro-benzenesulfonylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl]-4-
  - trifluoromethyl-benzamide,
  - 20 2-(3,5-Bis-trifluoromethyl-benzenesulfonamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-
  - carboxylic acid tert-butyl ester,
  - 2-(2,3-Dichloro-benzenesulfonamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic
  - acid tert-butyl ester,
  - 2-(3,5-Dichloro-benzenesulfonamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic
  - 25 acid tert-butyl ester, and
  - N-[5-(2-Cyclopentyl-acetyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl]-3,5-bis-
  - trifluoromethyl-benzenesulfonamide.

3. A compound according to any one of claims 1 or 2 of formula



4. A compound of any one of claims 1 to 3 in the form of a salt.
5. The use of an N-(3a,4,5,7,7a-hexahydro-thiazolo[5,4-c]pyridin-2-yl)-benzensulfonamide wherein the nitrogen atom of the pyridine is substituted, in the preparation of a medicament for the treatment of a disorder mediated by the action of steroid sulfatase, such as acne.
6. A method of treating disorders mediated by the action of steroid sulfatase comprising administering a therapeutically effective amount of a compound of any one of claims 1 to 4 to a subject in need of such treatment.
7. A pharmaceutical composition comprising a pharmaceutically effective amount of at least one compound of any one of claims 1 to 4 in association with at least one pharmaceutically acceptable excipient.
8. A compound of any one of claims 1 to 4 for use as a pharmaceutical.
9. A compound of any one of claims 1 to 4 in combination with at least one other pharmaceutically effective agent for use as a pharmaceutical, such as a pharmaceutical composition comprising a combination of at least one compound of any one of claims 1 to 4 with at least one other pharmaceutically effective agent.

- 20 -

**Abstract**

- 5 An N-(3a,4,5,7,7a-hexahydro-thiazolo[5,4-c]pyridin-2-yl)-benzensulfonamide wherein the nitrogen atom of the pyridinyl group is substituted, e.g. useful as a pharmaceutical.

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